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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,394	08/05/2005	Jonathan S Stamler	28195-508 NATL	2192

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
07/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,394	STAMLER ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page / 02/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on February 22, 2008.

Election/Restrictions

Applicant's election of Group I (claims 1-6) in the reply filed on February 22, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of Claims

Claims 1-8 are currently pending and are the subject of this office action.

Claim 7-8 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 22, 2008.

Claims 1-6 are presently under examination.

Priority

The present application is a 371 of PCT/US02/36138 filed on 12/02/2002, and claims priority to provisional application No. 60/336,175 filed on 12/06/2001.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (CAS accession # 1993:1375, corresponding to Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216), or Davies et. al. (CAS accession # 1998:302984, corresponding to Annals of Plastic Surgery (1998) 40:630-636).

Claim 1 recites a method for preventing necrosis in a pedicle flap or in any microvascular surgery, comprising topically applying to pedicle or other source of blood supply, a therapeutically effective amount of vasodilator composition containing NO or NO donor or prodrug that causes formation of nitrosothiol in tissue, optionally in combination with lidocaine.

For claim 1, Kreidstein et. al. teach the potential use of topical nitrovasodilators or NO donors for prevention and (or) treatment of skin flap ischemia (i.e. ischemic necrosis) (see abstract, last 4 lines). For claim 1, Davies et. al. teach that nitroglycerin (a NO donor) improves random-pattern skin flap survival significantly after mainstream cigarette smoke exposure in the rat. These results imply that pharmacological intervention with vasodilators may ultimately prove clinically useful for random-pattern skin flap salvage in the cigarette-smoking patient (see abstract).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Kreidstein et. al. (treating skin flap ischemia with NO donors) or Davies et. al. (the use of NO donors for skin flap survival)

with the motivation of better treating or preventing necrosis in a pedicle flap, thus resulting in the practice of claim 1 with a reasonable expectation of success.

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (CAS accession # 1993:1375, corresponding to Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216), or Davies et. al. (CAS accession # 1998:302984, corresponding to Annals of Plastic Surgery (1998) 40:630-636) as applied to claim 1 above, and further in view of Cederqvist et. al. (CAS accession # 1994:289800, corresponding to Biochemical Pharmacology (1994), 47:1047-1053).

Claims 2 and 3 further limit claim 1, wherein the vasodilator composition contains alkyl nitrite of molecular weight up to 10,000 (claim 2) or more specifically: ethyl nitrite (claim 3).

Kreidstein et. al. or Davies et. al. teach all the limitations of claims 2 and 3, except for the use of alkyl nitrites (ethyl nitrite in particular) as the vasodilator (or NO donor). However, Cederqvist et. al. teach that Ethyl nitrite (molecular weight less than 10,000) and organic nitrites in general are NO donors (see abstract).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Kreidstein et. al. (treating skin flap ischemia with NO donors) or Davies et. al. (the use of NO donors for skin flap survival) with the teachings of Cederqvist et. al. (Alkyl nitrites in general and ethyl nitrite in particular are NO donors) with the motivation of better treating or preventing necrosis in

a pedicle flap, thus resulting in the practice of claims 2 and 3 with a reasonable expectation of success.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (CAS accession # 1993:1375, corresponding to Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216), or Davies et. al. (CAS accession # 1998:302984, corresponding to Annals of Plastic Surgery (1998) 40:630-636) as applied to claim 1 above, and further in view of Stamler et. al. (US 5,770,645).

Claims 4 and 5 further limit claim 1, wherein the vasodilator (NO donor) composition contains S-nitrosothiol (claim 2) or more specifically: cyclodextrin NO (claim 5).

Kreidstein et. al. or Davies et. al. teach all the limitations of claims 4 and 5, except for the use of S-nitrosothiol (cyclodextrin NO) as the vasodilator (or NO donor). However, Stamler et. al. teach that S-nitrosylated cyclodextrins (a type of cyclodextrin NO) are NO donors (see column 2, first paragraph).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Kreidstein et. al. (treating skin flap ischemia with NO donors) or Davies et. al. (the use of NO donors for skin flap survival) with the teachings of Stamler et. al. (cyclodextrin NO are NO donors) with the motivation of better treating or preventing necrosis in a pedicle flap, thus resulting in the practice of claims 4 and 5 with a reasonable expectation of success.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kreidstein et. al. (CAS accession # 1993:1375, corresponding to Canadian Journal of Physiology and Pharmacology (1992) 70:1208-1216), or Davies et. al. (CAS accession # 1998:302984, corresponding to Annals of Plastic Surgery (1998) 40:630-636) as applied to claim 1 above, and further in view of Wang et. al. (CAS accession # 2000094431, corresponding to Journal of Cardiovascular Pharmacology (2000) 35:73-77).

Claim 6 further limits claim 1, wherein the vasodilator (NO donor) composition contains a metal nitrosyl.

Kreidstein et. al. or Davies et. al. teach all the limitations of claim 6, except for the use of metal nitrosyl as the vasodilator (or NO donor). However, Wang et. al. teach that metal nitrosyl are NO donors (see title and abstract).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Kreidstein et. al. (treating skin flap ischemia with NO donors) or Davies et. al. (the use of NO donors for skin flap survival) with the teachings of Wang et. al. (metal nitrosyl are NO donors) with the motivation of better treating or preventing necrosis in a pedicle flap, thus resulting in the practice of claim 6 with a reasonable expectation of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is

(571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1611
July 10, 2008

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615